THE CONTENT OF SULFHYDRIL GROUPS IN THE BLOOD SERUM IN EXPERIMENTAL RENAL HYPERTENSION AND THE REDUCTION OF HYPERTENSION BY PROLONGED IRON ADMINISTRATION

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We have investigated the problem of the influence of prolonged administration of iron (in the form of ferrous ammonium citrate) on the course of experimental hypertension in rabbits. Under these circumstances experimental confirmation was obtained of Kh. S. Koshtoyants's hypothesis of the possible hypotensive effect of injections of iron as a stimulator of the biosynthesis of ferritin — a specific iron-containing protein which appears in the blood in hypertension at the stage of stabilization of the pressure and lowers the sensitivity of the vessels to adrenalin.

It has been shown [3] that the level of experimental hypertension may be lowered by the prolonged administration of iron, and moreover that the hypotensive effect may be explained by stimulation of the biosynthesis of ferritin and the intensive functional utilization of this substance by the body.

There are isolated, indirect reports in the literature that sulfhydril compounds are concerned in a chain of specific enzymochemical reactions which play a role in the pathogenesis of the hypertensive state. It has been found that the vasodepressor properties of ferritin and the interaction of ferritin with adrenalin depend on the state of the SH-groups of the ferritin [4, 6].

B. N. Manukhin [2] showed that the tissue SH-groups play a definite part in the mechanism of action of sympathetico-adrenal factors.

In view of these findings, and at the suggestion of Kh. S. Koshtoyants, we conducted the present investigation, devoted to an analysis of the content of SH-groups in the blood serum during the development of experimental hypertension, and in the course of the lowering of the blood pressure by our method of prolonged administration of iron.

EXPERIMENTAL METHOD

In the quantitative estimation of the SH-groups in the blood serum we used the method of amperometric titration of Kolthoff and his co-workers [5], as modified by T. M. Turpaev and S. N. Nistratova. A volume of 0.5 ml of serum, obtained immediately before titration, was mixed with 30 ml of 0.9% NaCl and titrated with 0.001N $HgCl_2$. To record the diffused current we used a microammeter with a sensitivity of $1 \cdot 10^{-8}$ a. In successive titrations of the same sample, the error did not exceed 4%.*

Experimental hypertension was induced in rabbits by partial clamping of the renal arteries. Iron was injected intravenously in the form of a solution of ferrous ammonium citrate (in a dose of 1.5 mg iron per kg

*I express my gratitude to S. N. Nistratova for her help in mastering the technique of amperometric titration of SH-groups.

body weight) on the day before the operation to clamp the renal arteries, and daily thereafter throughout the whole period of observation. Blood for analysis was taken from the marginal vein of the ear, 2-3 times before operation as a rule, and then once every 10-15 days throughout the experiment (30-240 days after operation).

Four groups of rabbits were investigated: the 1st group (10 animals) were normal rabbits; the 2nd group (15 animals) were rabbits with experimental renal hypertension (blood pressure 25-35% above the normal level); the 3rd group (12 animals) were rabbits with experimental renal hypertension and receiving iron (the blood pressure in these animals was 20-40% below that of the animals of the 2nd group); and the 4th group (10 animals) were normal rabbits receiving iron.

EXPERIMENTAL RESULTS

From our study of the content of SH-groups in the blood serum of 56 normal rabbits we found that it varied between wide limits – 38-78 μM/100 ml – being on the average 55.8 μM/100 ml. These findings were in agreement with those of Weissman and his co-workers [7], who showed that the content of SH-groups in human blood serum was 48.8-59.0 μM/100 ml.

From repeated analyses carried out over a long period of time (2 months), it followed that the level of SH-groups in the blood serum was a reasonably constant value for any one animal (given the same physiological conditions). In a group of 10 normal rabbits (1st group) the maximum variation was on the average ± 6.8%.

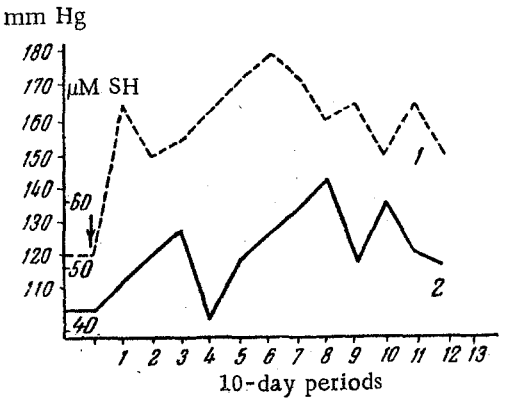

Fig. 1. Changes in the blood pressure (1) and content of sulfhydril groups (2) during the development of experimental hypertension. Rabbit No. 128. ↓ – moment of operation to clamp the renal arteries.

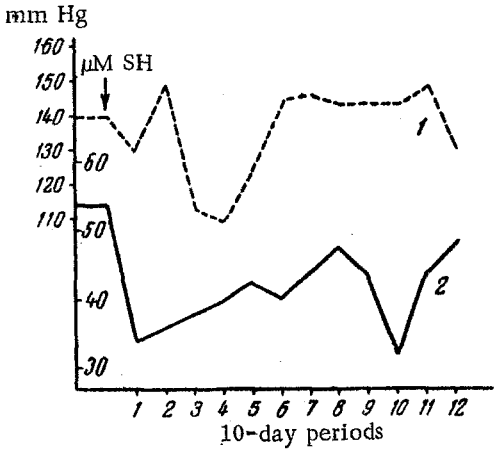

Fig. 2. Changes in the blood pressure (1) and the content of sulfhydril groups (2) during the development of experimental hypertension in association with the prolonged administration of iron. Rabbit No. 141. ↓ – moment of operation of to clamp the renal arteries.

During the development of experimental renal hypertension (2nd group of rabbits; Fig. 1) in 80% of cases an increase was observed in the content of SH-groups which at certain times reached 120-150% of the initial level, i.e., was considerably higher than the normal variations. Sometimes (in 50% of cases) in the first days after operation or, conversely, after 3-4 months, in the stage of stabilization and of a slight fall in the pressure, a decrease took place in the level of the SH-groups to 70-90% of normal; as a rule, however, it was of very brief duration. No clear relationship was found between the level of the blood pressure and the content of SH-groups in the blood serum.

In the 3rd group of animals (rabbits with experimental renal hypertension and receiving iron), in 100% of cases a fall in the content of SH-groups to 60-85% of normal was observed; under these circumstances the level usually remained low throughout the whole period of observation (Fig. 2). In 30% of cases slight rises in the level of the SH-groups were recorded at different times after operation, but these values very soon fell again below their original level. If, therefore, during the development of experimental hypertension there was an obvious tendency for the content of SH-groups to rise, then when the level of the hypertension fell as the result of the prolonged administration of iron, there was a clearly marked fall in the content of SH-groups in the blood serum.

Injections of iron into normal animals (4th group of rabbits) in 80% of cases caused a fall in the content of SH-groups in the blood serum to 80-85% of their initial level, i.e., the effect was shown less clearly than after injection of iron into rabbits with experimental hypertension.

The results obtained led to the conclusion that sulfhydril compounds are one of the links in the complex chain of enzymochemical reactions which play a role in the pathogenesis of the hypertensive state.

B. N. Manukhin [2] showed that the action of the sympathetico-adrenal system depends on the SH-groups of the tissues: during disulfidization the sensitivity to the adrenal factor falls, whereas the presence of substances preventing oxidation of SH-groups leads to stimulation of the action of adrenalin.

Bearing in mind the numerous reports of the role of the sympathetico-adrenal system in the development of hypertension, and also the work cited above on the role of SH-groups in the ferritin — adrenalin system, the role of SH-groups may be represented in the most general terms as follows. Excess of SH-groups in the blood, observed during elevation of the blood pressure, stabilizes adrenalin, increases the sensitivity of the vessels to it, and thereby provides for maintenance of the blood pressure at a high level. On the other hand, a decrease in the content of free SH-groups, caused by a shift in the metabolic processes associated with the intensified biosynthesis of ferritin, leads to intensive oxidation of adrenalin, to lowering of sensitivity to it and, as a result, to some decrease in the level of the hypertension. Indirect confirmation of this hypothesis may be given by the findings of M. Yu. Gaisinskaya [1], who showed that the blood serum has a stabilizing influence on adrenalin, and moreover, that the stabilizing systems become more active in hypertensive disease and in experimental renal hypertension.

The zigzag character of the curve of content of SH-groups during the development of hypertension (2nd and 3rd groups of rabbits; see Figs. 1 and 2) may evidently be explained by the complex interaction between two processes: a pathological, leading to a rise in the pressure and associated with an increase in the content of SH-groups, and a protective, causing a fall in the pressure and accompanied by a lowering of the level of SH-groups in the blood serum. Under these circumstances the pathological process dominates in the animals of the 2nd group, and in the animals of the 3rd group, receiving iron, the protective process is more in evidence. The fact that administration of iron causes a greater reaction in rabbits with hypertension than in normal rabbits shows that the character of the protective reaction in the first case is fairly complex and cannot be reduced to simple stimulation of the biosynthesis of ferritin in the body.

SUMMARY

The authors examined the content of SH-groups in the blood serum of rabbits in development of experimental renal hypertension and in reduction of the latter by chronic iron administration. It was demonstrated that hypertension is accompanied with the rise of the SH-groups content in the blood serum, while in decrease of hypertension by 20-40% as a result of chronic iron administration, the content of the SH-groups becomes lower than its initial value. The data obtained are being considered in connection with the adrenalin and ferritin metabolism in hypertension.

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